PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 473/06, A61K 31/52 | A1

(11) International Publication Number: WO 92/05175

(43) International Publication Date: 2 April 1992 (02.04.92)

(21) International Application Number: PCT/GB91/01633

(22) International Filing Date: 23 September 1991 (23.09.91)

(30) Priority data:
9020959.4 26 September 1990 (26.09.90) GB

(71) Applicant *(for all designated States except US)*: BEECHAM GROUP PLC [GB/GB]; SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).

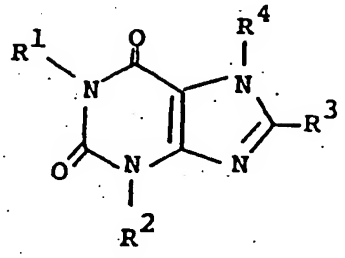
(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : BUCKLE, Derek, Richard [GB/GB]; SMITH, David, Glynn [GB/GB]; FENWICK, Ashley, Edward [GB/GB]; SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

(74) Agent: RUTTER, Keith; Corporate Patent, SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: XANTHINE DERIVATIVES



(I)

(57) Abstract

A compound of formula (I) or, if appropriate, a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, wherein R^1 and R^2 each independently represent a moiety of formula (a): $-(CH_2)_m-A$, wherein m represents zero or an integer 1, 2 or 3 and A represents a substituted or unsubstituted cyclic hydrocarbon radical; R^3 represents NO_2, a halogen atom, a hydroxy group, an alkoxy group or a methyl group substituted with 1 or 2 groups of formula CO_2R, wherein R in each group is independently hydrogen or alkyl or a group of formula O-L-A^1 wherein L is a bond or a linking group and A^1 is a saturated or unsaturated heterocyclic group, or R^3 represents a group of formula NR^sR^t, wherein R^s and R^t each independently represent hydrogen, alkyl, aralkyl, an unsaturated heterocyclic group or R^s and R^t together with the nitrogen to which they are attached form an unsaturated heterocyclic group; and R^4 represents an alkyl, aralkyl or an (unsaturated heterocyclyl)alkyl group; a process for preparing such a compound, a pharmaceutical composition containing such a compound and the use of such a compound or composition in medicine.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU+	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE*	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

Xanthine derivatives.

The present invention relates to certain novel compounds having pharmacological activity, to a process for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

Molecular Pharmacology, Volume 6, No. 6, 1970, p.597-603 discloses 1,3-dimethyl-8-nitro-xanthine. This compound is disclosed as having lipolytic activity. Ann. Chim. 47, 362-365 (1957) discloses 1,3-dimethyl-8-amino-xanthine and a process by which it may be prepared. No pharmacological utility is disclosed for this compound. Drug Res. 27(1) Nr 19, 1977, pages 4-14, Van K.H. Klingler discloses certain 1,3-dimethyl-8-substituted xanthines as intermediates solely in the synthesis of phenylethyl aminoalkyl xanthines. Drug Res. 31 (11), Nr. 12, 1981, R.G. Werner et al, pages 2044-2048 discloses certain 1,3-dimethyl-8-substituted xanthines. No pharmacological activity is disclosed for these compounds. European Patent Application, Publication Number 0369744 also discloses certain 1,3- or 1,3,7- 8-H cycloalkylalkylene xanthines, for use inter alia as bronchodilators in the treatment of asthma. European Patent Application, Publication Number 0389282 also discloses certain 8-substituted 1,3- dicycloalkylalkylene xanthines, for use inter alia in the treatment or prophylaxis of disorders associated with increased numbers of eosinophils.

It has now surprisingly been discovered that a novel series of substituted xanthines, some of which are generically but not specifically disclosed in EP 0389282, are indicated to be particularly effective as inhibitors of induced blood eosinophilia and that they are therefore potentially of particular use in the treatment and/or prophylaxis of disorders associated with increased numbers of eosinophils, such as asthma, and allergic disorders associated with atopy, such as urticaria, eczema and rhinitis.

In addition these compounds show activity as phosphodiesterase inhibitors:

These compounds are indicated to have bronchodilator activity and thus to be of potential use in the treatment of disorders of the respiratory tract,

such as reversible airways obstruction and asthma.

These compounds have a protective effect against the consequences of cerebral metabolic inhibition. The said compounds improve data acquisition or retrieval following transient forebrain ischaemia and are therefore useful in the treatment of cerebral vascular and neuronal degenerative disorders associated with learning, memory and cognitive dysfunctions including cerebral senility, multi-infarct dementia, senile dementia of the Alzheimer type, age associated memory impairment and certain disorders associated with Parkinson's disease.

These compounds are also indicated to have neuroprotectant activity. They are therefore useful in the prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events, including cerebral ischaemia due to cardiac arrest, stroke and also after cerebral ischaemic events such as those resulting from surgery and/or during childbirth. In addition treatment with these compounds is indicated to be of benefit for the treatment of functional disorders resulting from disturbed brain function following ischaemia.

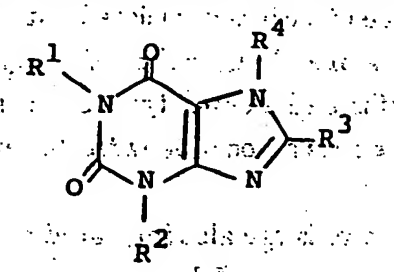
These compounds are also active in increasing the oxygen tension in ischaemic skeletal muscle. This property results in an increase in the nutritional blood flow through ischaemic skeletal muscle which in turn indicates that the compounds of the invention are of potential use as agents for the treatment of peripheral vascular disease such as intermittent claudication.

These compounds are also of potential use in the treatment of proliferative skin disease in human or non-human mammals.

In addition these compounds may also have potential as inhibitors of the production of tumour necrosis factor (TNF) and hence have potential for the treatment of human immunodeficiency virus (HIV), acute immune deficiency syndrome (AIDS), rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, pulmonary inflammatory disease, bone resorption diseases, reperfusion

injury, graft vs. host reaction, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to AIDS, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

Accordingly, the invention also provides a compound of formula (I):



(I)

or if appropriate a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 each independently represent a moiety of formula (a):

$$-(CH_2)_m\text{-}A \qquad (a)$$

wherein m represents zero or an integer 1, 2 or 3 and A represents a substituted or unsubstituted cyclic hydrocarbon radical;

R^3 represents NO_2, a halogen atom, a hydroxy group, an alkoxy group or a methyl group substituted with 1 or 2 groups of formula CO_2R wherein R in each group is independently hydrogen or alkyl or a group of formula O-L-A^1 wherein L is a bond or a linking group and A^1 is a saturated or unsaturated heterocyclic group, or R^3 represents a group of formula NR^sR^t wherein R^s and R^t each independently represent hydrogen, alkyl, aralkyl, an unsaturated heterocyclic group or R^s and R^t together with the nitrogen to which they are attached form an unsaturated heterocyclic group; and

R^4 represents an alkyl, aralkyl or an (unsaturated heterocyclyl)alkyl group.

Suitably, A represents a substituted or unsubstituted alicyclic hydrocarbon radical.

Suitably, A is unsubstituted. Favourably, A represents a substituted or unsubstituted C_{3-8} cycloalkyl group, especially a C_{3-6} cycloalkyl group.

In particular, A represents a substituted or, preferably, unsubstituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

Favourably, A represents a cyclopropyl group or a cyclobutyl group.

Particular aralkyl groups are benzyl and naphthylmethyl groups.

Particular substituents for the aryl moiety of any aralkyl group include NO_2 and alkoxy, especially NO_2 and methoxy.

When R^s and/or R^t represents aralkyl, examples include benzyl and nitrobenzyl, especially 2-nitrobenzyl.

When R^4 represents aralkyl examples include methoxybenzyl, such as 4-methoxybenzyl; trimethoxybenzyl, such as 3,4,5-trimethoxybenzyl; nitrobenzyl, such as 2- or 4-nitrobenzyl; and naphthylmethyl.

When L represents a bond, the saturated or unsaturated heterocyclic group represented by A^1 is attached by a ring carbon atom to the O atom of the group O-L-A^1.

When L represents a bond, preferred carbon linked heterocyclic groups represented by A^1 are single ring heterocyclic groups having 6 ring atoms, which ring atoms comprise 1 or 2, especially 1, heteroatoms, selected from O or N, preferably N; particular examples include piperidinyl groups.

When L represents a linking group, a suitable linking group is a C_{1-6} alkylene chain, optionally interrupted by an oxygen atom.

An Example of a linking group L is $-(CH_2)_2-O-(CH_2)_2-$.

When L represents a linking group, suitable heterocyclic groups represented by A^1 are single ring heterocyclic groups having 5- or 6- ring atoms which ring atoms comprise 1 or 2, especially 1, heteroatoms selected from O or N, preferably N; particular examples include piperazinyl groups, especially N-piperazinyl groups.

Particular substituents for the heterocyclic groups represented by A^1

include aralkyl, especially benzyl, and alkyl carbonyl wherein the alkyl group may be substituted or unsubstituted, a particular substituent for the said alkyl group being a carboxy group or an alkyl ester thereof. Examples of substituents for the heterocyclic group represented by A^1 are benzyl and $-CO(CH_2)_2CO_2H$ or an ester thereof.

When either R^s or R^t represent an unsaturated heterocyclic group, particular groups are single ring, 6-membered heterocyclic groups which ring atoms comprise 1 or 2, preferably 1, heteroatoms selected from O or N, preferably N;suitable examples are heteroaryl groups such as pyridyl.

When R^s and R^t together with the nitrogen atom to which they are attached form an unsaturated heterocyclic group, suitable heterocyclic groups are single ring, 5- or 6- membered heterocyclic groups optionally comprising 1 or 2, preferably 1, additional heteroatoms in the ring; particular examples include imidazolyl groups.

When R^4 represents an (unsaturated heterocyclyl)alkyl group, suitable examples are heteroarylalkyl groups such as heteroarylmethyl groups, the unsaturated heterocyclyl group suitably being a single ring, 6-membered heterocyclyl group which ring atoms comprise 1 or 2, preferably 1, heteroatoms selected from O or N, preferably N; particular examples include pyridylmethyl groups.

Suitably, R^3 represents nitro, a halogen atom, an alkoxy group, such as an ethoxy group, or a group NR^sR^t wherein R^s and R^t each independently represent hydrogen or alkyl, especially hydrogen.

When R^3 represents R^sR^t, in one particular aspect R^s represents hydrogen and R^t represents alkyl, aralkyl or an unsubstituted heterocyclic group.

When R^4 is alkyl suitable examples include C_{1-4} alkyl such as methyl.

Preferably, A represents a cyclopropyl group.

Preferably R^3 represents NH_2.

Suitably R^4 represents an alkyl or aralkyl group. Preferably R^4 represents an aralkyl group, especially a benzyl group. Favourably, m represents 1.

Suitable pharmaceutically acceptable solvates are those used conventionally such as hydrates.

Suitable pharmaceutically acceptable salts are pharmaceutically acceptable base salts and pharmaceutically acceptable acid addition salts. Suitable pharmaceutically acceptable base salts of the compounds of formula (I) include base salts including metal salts, such as alkali metal salts for example sodium salts, or organic amine salts such as that provided with ethylenediamine.

Suitable acid addition salts of the compounds of formula (I) are the acid addition salts including pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, fartrate, maleate, citrate, succinate, benzoate, ascorbate, methanesulphonate, α-keto glutarate, α-glycerophosphate and glucose-1-phosphate. Preferably the acid addition salt is a hydrochloride salt.

The pharmaceutically acceptable salts and/or solvates of the compounds of formula (I) are prepared using conventional procedures.

When used herein the term 'cyclic hydrocarbon radical' includes single ring and fused ring, alicyclic hydrocarbons comprising up to 8 carbon atoms in each ring, suitably up to 6 carbon atoms, for example 3, 4, 5 or 6 carbon atoms.

Suitable optional substituents for any cyclic hydrocarbon radical includes a C_{1-6} alkyl group or a halogen atom.

When used herein the term 'alkyl' (whether used alone or when used as part of another group for example as in an alkylcarbonyl group) includes straight and branched chain alkyl groups, containing from 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms, for example methyl, ethyl, propyl or butyl. Optional substituents for alkyl groups include those mentioned

herein for aryl groups.

When used herein the term 'aryl' (whether used alone or when used as part of other groups for example as in an aralkyl group) includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, halo alkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

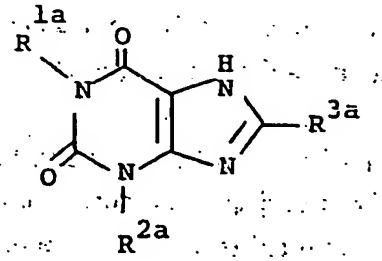
The term 'heterocyclic' or 'heterocyclyl' when used herein refers to groups comprising single or fused rings which rings each comprise 4 to 7, suitably 5 or 6 ring atoms, which ring atoms comprise up to 4 hetero atoms selected from O, N or S.

Optional substituents for any 'heterocyclic' or 'heterocyclyl' group include alkyl, alkoxy, halo, carboxy or an alkyl ester thereof, aralkyl or alkyl carbonyl wherein the alkyl group may be substituted or unsubstituted.

When used herein the expression 'proliferative skin diseases' means benign and malignant proliferative skin diseases which are characterized by accelerated cell division in the epidermis, dermis or appendages thereto, associated with incomplete tissue differentiation. Such diseases include: psoriasis, atopic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, allergic contact dermatitis, basal and squamous cell carcinomas of the skin, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant sun induced keratosis, non-malignant keratosis, acne, and seborrheic dermatitis in humans and atopic dermatitis and mange in domesticated animals.

The compounds of formula (I) are preferably in pharmaceutically acceptable form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%.

The invention further provides a process for the preparation of a compound of formula (I), which process comprises reacting a compound of formula (II):



(II)

wherein R^{1a} represents R^1, as defined in relation to formula (I), or a group convertible to R^1 and R^{2a} represents R^2, as defined in relation to formula (I), or a group convertible thereto and R^{3a} represents R^3 as defined in relation to formula (I), or a group convertible thereto, with a compound of formula (III):

$$R_4\text{-}L^1 \qquad \text{(III)}$$

wherein R^4 is as defined in relation to formula (I) and L^1 represents a leaving group; and thereafter, if required carrying out one or more of the following optional steps:

(i) converting any group R^{1a} to R^1 and/or R^{2a} to R^2 and/or R^{3a} to R^3;

(ii) converting a compound of formula (I) into a further compound of formula (I);

(iii) converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

A suitable leaving group L^1 is a halo atom, for example a bromine or chlorine atom.

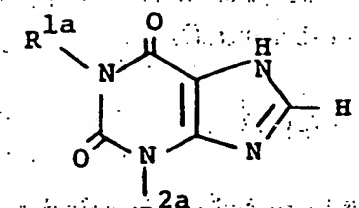
The reaction between compounds of formulae (II) and (III) may be carried out using conventional alkylation conditions, for example in an aprotic solvent, such as dimethylformamide, tetrahydrofuran or dimethylsulphoxide, at any temperature providing a suitable rate of formation of the required product, for example in the range of from 0°C to

100°C, conveniently at ambient temperature.

Preferably, in the reaction between compounds (II) and (III), the compound of formula (II) is in an activated form, suitably in an anionic form such as a salted form, for example an alkali metal salted form.

The activated form of the compound of formula (II) is conveniently prepared by treating a compound of formula (II) with a base, suitably an alkali metal alkoxide, for example potassium t-butoxide, or an alkali metal hydride, for example sodium hydride.

A compound of formula (II) may be prepared by reacting a compound of formula (IV):



(IV)

wherein R^{1a} represents R^1, as defined in relation to formula (I), or a group convertible to R^1 and R^{2a} represents R^2, as defined in relation to formula (I), or a group convertible thereto, with a reagent capable of substituting the C-8 hydrogen of the compound of formula (IV) with a group R^{3b} wherein R^{3b} represents R^{3a}, as defined above in relation to formula (II), or a group convertible thereto; and thereafter, if required carrying out one or more of the following optional steps:

(i) converting any group R^{1a} to R^1 and/or R^{2a} to R^2;

(ii) when R^{3b} is not R^{3a}, converting R^{3b} to R^{3a}.

For compounds of formula (II) wherein R^{3a} represents nitro, R^{3b} preferably represents R^{3a} i.e. nitro.

For compounds of formula (II) wherein R^{3a} represents other than nitro, R^{3b} preferably represents a group convertible to R^{3a}.

One preferred group R^{3b} is a nitro group which may then if required be

converted to groups R^{3a} other than nitro.

Suitable reagents for substituting the C-8 hydrogen of the compound of formula (IV) with a group R^{3b} are the appropriate conventional reagents.

The conditions of reaction for the substitution of the C-8 hydrogen of the compound of formula (IV) will of course depend upon the particular reagent chosen, and in general the conditions used will be those which are conventional for the reagent used.

One particularly suitable reagent is a nitrating agent.

The nitration of compound (II) may be carried out using any suitable, conventional nitrating agent, for example a nitric acid/acetic acid mixture in an inert solvent, such as dichloromethane, at any temperature providing a convenient rate of formation of the required product, conveniently at ambient temperature.

In one convenient form of the abovementioned process the compound of formula (IV) is reacted with a suitable nitrating agent to provide a compound of formula (II) wherein R^{3a} represents a nitro group and then converting the nitro group into a halogen atom or a group of the abovedefined formula $-NR^sR^t$, suitably via the halogen atom.

For example, when R^{3a} represents a nitro group, suitable conversions of the nitro group into another group R^{3a} include the following:

(i) converting the nitro group into a halogen atom;

(ii) converting the nitro group into an amine group;

(iii) converting the nitro group into a halogen atom followed by conversion of the halogen atom into the above defined group $-NR^sR^t$;

(iv) converting the nitro group into a halogen atom and thereafter converting the halogen atom into a methyl group substituted with 1 or 2 groups of formula CO_2R, wherein R is as defined above.

(v) converting the nitro group into a halogen atom and thereafter converting the halogen atom into the above defined group O-L-A^1.

(vi) converting the nitro group into an amino group and thereafter alkylating the amino group to provide the above defined group -NR^sR^t; and

(vii) converting the nitro group into an halogen atom, and thereafter converting the halogen atom into a hydroxy group or an alkoxy group.

A nitro group may be converted into a halogen atom by using any convenient halogenating agent.

One suitable halogenating agent is a hydrogen halide, suitably reacted in aqueous conditions for example by using concentration hydrochloric acid at an elevated temperature, for example in the range of from 50 to 150°C.

A further suitable halogenating agent is a phosphorous oxyhalide, such as phosphorous oxychloride or phosphorous oxybromide, which may be reacted in any suitable solvent, such as dimethylformamide, suitably at an elevated temperature for example in the range of from 50°C to 150°C.

A nitro group may conveniently be converted into an amino group by conventional reduction methods for example by using tin powder and concentrated hydrochloric acid at ambient temperature or by using sodium dithionite in aqueous methanol at ambient temperature.

When R^{3a} represents a halogen atom, it may be converted into a methyl group substituted with 1 or 2 groups of formula CO_2R wherein R is as defined above, by reacting the required compound of formula (II) wherein R^{3a} is halogen, with the appropriate mono or bis malonate wherein the esterifying moiety is a group R as defined above, in the presence of a base such as sodium hydride in an aprotic solvent at any temperature providing a suitable rate of formation of the required product, conveniently at an elevated temperature such as in the range of 40°C to 120°C, for example 80°C.

When R^{3a} in the compound of formula (II) represents a halogen atom it

may be converted into a group -O-L-A^1, wherein L and A^1 are as defined in relation to formula (I), by reaction with a reagent of formula (V) or, preferably, an activated form thereof:

$$A^1\text{-}L\text{-}OH \qquad (V)$$

wherein A^1 and L are as defined above.

The reaction between the compound of formula (II) when R^{3a} is halogen and the compound of formula (V) may be carried out under analogous conditions to the above described reaction between compounds of formulae (II) and (III).

Suitable activated forms of the compound of formula (V) are salted forms such as alkali metal salted forms.

In one convenient aspect the activated form of compounds of formula (V) are prepared by treating the compound of formula (III) with a base, suitably an alkali metal base such as those referred to above.

When R^{3a} in the compound of formula (II) represents a halogen atom it may be converted into a group -NR^sR^t by reacting with a reagent of formula (VI):

$$HNR^sR^t \qquad (VI)$$

wherein R^s and R^t are as defined above.

The reaction between the compound of formula (II) and the compound of formula (VI) may be carried out in any suitable solvent, such as toluene, at any temperature providing a convenient rate of formation of the product, but suitably at an elevated temperature, such as in the range of from 50° to 180°C, at atmospheric or an elevated pressure.

Suitable alkylation methods for use in the abovementioned conversions include those used conventionally in the art, for example methods using halides, preferably iodides, in the presence of a base such as potassium carbonate in any convenient solvent for example acetonitrile or toluene.

In the conversion (vi), the nitro group may be converted into the halogen atom as described above. The conversion of the halogen atom into an alkoxy group may be effected by any conventional alkoxylation procedure, for example treating the halogen with a source of alkoxy ions, such as a sodium alkoxide.

Suitable conversions of a compound of formula (I) into another compound of formula (I) generally include converting one group R^3 into another group R^3.

Conversions of one group R^3 into another group R^3 include the following:

(i) the abovementioned conversions of R^3 when nitro or halogen into other groups R^3; and

(ii) the conversion of one group NR^sR^t into another group NR^sR^t.

An example of a conversion of one group NR^sR^t into another group is that wherein NR^sR^t represents a piperidinyloxy group, which may thereafter be converted into an (N-4-oxo-butanoic acid) piperidinyloxy group, by treatment with succinic hydride in dry dimethylformamide, or into an (N-benzyl) piperidinyloxy group, by conventional benzylation procedures.

A compound of formula (IV) may be prepared according to methods disclosed in EP 0369744.

Suitable values for R^{1a} and R^{2a} include R^1 and R^2 respectively or nitrogen protecting groups such as silyl groups.

When R^{1a} or R^{2a} represents other than R^1 or R^2 repectively, the abovementioned conversions of R^{1a} into R^1 and R^{2a} to R^2 may be carried out using the appropriate conventional procedure.

The protection of any reactive group or atom, such as any of the xanthine nitrogen atoms may be carried out at any appropriate stage in the aforementioned processes. Suitable protecting groups include those used conventionally in the art for the particular group or atom being protected,

for example suitable protecting groups for the xanthine nitrogen atoms are silyl groups, especially trialkyl silyl groups such as t-butyl dimethyl silyl or trimethyl silyl groups.

Protecting groups may be prepared and removed using the appropriate conventional procedure:

For example, N-benzyl protecting groups may be prepared by treating the appropriate compound of formula (II) with benzyl chloride in the presence of a base such as triethylamine, bases such as potassium t-butoxide may also be used . The N-benzyl protecting groups may be removed by catalytic hydrogenation over a suitable catalyst, such as palladium on activated charcoal, in a suitable solvent, such as ethanol conveniently at an elevated temperature, or by treatment with anhydrous aluminium chloride in dry benzene at ambient temperature. Trialkylsilyl protected nitrogen groups may be prepared by treating the appropriate compound with a trialkylsilyl halide, for example trimethylsilyl chloride, in the presence of a base such as potassium t-butoxide. The N-trialkylsilyl protecting group may be removed by mild basic hydrolysis or by treatment with a source of fluoride ions such as tetrabutylammoniumfluoride.

Compounds of formulae (II) are novel compounds and as such form part of the present invention.

Compounds of formula (III), (V), and (VI) are known compounds or are prepared according to methods used to prepare known compounds for example those disclosed in J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties: the present invention accordingly provides a compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

Thus the present invention provides a compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for use in the treatment of

and/or prophylaxis of disorders associated with increased numbers of eosinophils, such as asthma, and allergic disorders associated with atopy, such as urticaria, eczema and rhinitis.

In a further aspect the present invention also provides a compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for use as a phosphodiesterase inhibitor.

In a particular aspect, as indicated hereinbefore, the present invention provides a compound of formula (I) or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for use in the treatment of disorders of the respiratory tract, such as reversible airways obstruction and asthma.

In a further particular aspect, the present invention provides a compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for use in the treatments mentioned hereinbefore, such as cerebral vascular and neuronal denerative disorders associated with learning, memory and cognitive dysfunctions, peripheral vascular disease or proliferate skin disease or for the prophylaxis of disorders associated with neuronal degeneration resulting from ischaemic events or for the inhibition of the production of tumour necrosis factor in for example the treatment of human immunodeficiency virus.

A compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier.

The active compound may be formulated for administration by any suitable route, the preferred route depending upon the disorder for which

treatment is required, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations

may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

Compositions may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 microns, such as from 0.1 to 50 microns, preferably less than 10 microns, for example from 1 to 10 microns, 1 to 5 microns or from 2 to 5 microns. Where appropriate, small amounts of other anti-asthmatics and bronchodilators, for example sympathomimetic amines such as isoprenaline, ispetharine, salbutamol, phenylephrine and ephedrine; corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing.

Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate

uniform distribution of the compound.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

Compounds of formula (I), or if appropriate a pharmaceutically acceptable salt thereof, may also be administered as a topical formulation in combination with conventional topical excipients.

Topical formulations may be presented as, for instance, ointments, creams or lotions, impregnated dressings, gels, gel sticks, spray and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

Suitable cream, lotion, gel, stick, ointment, spray or aerosol formulations that may be used for compounds of formula (I) or if appropriate a pharmaceutically acceptable salt thereof, are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics and cosmetics, such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, and the British and US Pharmacopoeias.

Suitably, the compound of formula (I), or if appropriate a pharmaceutically acceptable salt thereof, will comprise from about 0.5 to 20% by weight of the formulation, favourably from about 1 to 10%, for example 2 to 5%.

The dose of the compound used in the treatment of the invention will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and the relative efficacy of the compound. However, as a general guide suitable unit doses may be 0.1 to 1000mg, such as 0.5 to 200, 0.5 to 100 or 0.5 to 10 mg, for example 0.5, 1, 2, 3, 4 or 5 mg; and such unit doses may be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total daily dosage for a 70kg adult is in the range of about 0.1 to 1000 mg, that is in

the range of about 0.001 to 20 mg/kg/day, such as 0.007 to 3, 0.007 to 1.4, 0.007 to 0.14 or 0.01 to 0.5 mg/kg/day, for example 0.01, 0.02, 0.04, 0.05, 0.06, 0.08, 0.1 or 0.2 mg/kg/day; and such therapy may extend for a number of weeks or months.

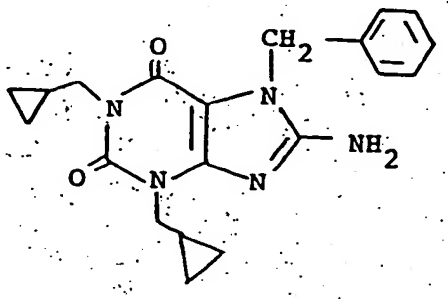
When used herein the term 'pharmaceutically acceptable' encompasses materials suitable for both human and veterinary use.

No toxicological effects have been established for the compounds of formula (I) in the abovementioned dosage ranges.

The following pharmacological data and examples illustrate the invention. The following preparations illustrate the preparation of intermediates to the novel compounds of formula (I).

Example 1

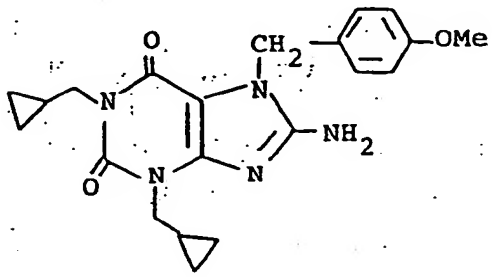
8-Amino-7-benzyl-1,3-di(cyclopropylmethyl)xanthine



Potassium t-butoxide(0.12g,1.1mmole)was added to a solution of 8-amino-1,3-di(cyclopropylmethyl)xanthine (0.27g,1mmole) in DMF(3ml) and the resulting mixture was stirred for 1hr at ambient temperature. Benzyl bromide (0.24ml,2mmole) was added to the dark orange/red solution which turned cherry red. After stirring for 1hr at ambient temperature the reaction mixture was added to ethyl acetate(80ml)and the organic solution washed with water(2x25ml), dried($MgSO_4$)and the solvent removed under reduced pressure to give a red solid(0.43g). Chromatography on silica (acetone/hexane 1:5) gave 8-amino-7-benzyl-1,3-di(cyclopropylmethyl) xanthine(0.31g,84%),m.p.158°C; ν_{max} (KBr) 3369(w), 3330(w), 1691(m),1639(s),1526(m) and 1432(m)cm^{-1}; $\delta(CDCl_3)$ 0.39-0.52(8H,m),1.25-1.36(2H,m), 3.89 (4H,t(overlapping d), J=6.5H_z),4.66(2H,brs),5.39(2H,s), 7.26-7.41 (5H,m); m/e 365(M^+,100%),91(60),214(30), 55(20),220(11), 337(8);
Found: C, 65.43; H, 6.15; N, 19.10. $C_{20}H_{23}N_5O_2$requires C, 65.73; H, 6.34; N, 19.17%.

Example 2

8-Amino-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-xanthine

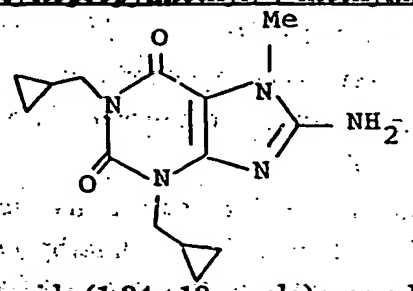


Potassium t-butoxide(1.34g,12mmole)was added to a solution of 8-amino-1,3-di(cyclopropylmethyl)xanthine (2.7g,10mmole)in DMF(25ml)and the resulting mixture was stirred for 0.5hr at ambient temperature. 4-Methoxybenzyl chloride(1.56g,1.35ml,10mmole) was added to the red solution which lightened to an orange colour. After stirring for 1hr at ambient temperature the mixture was added to ethyl acetate (200ml), washed with dilute hydrochloric acid(50ml),water(50ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a solid which was chromatographed on silica (hexane/acetone, gradient)to give 8-amino-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl) xanthine (2.55,64%) m.p.176°C, ν_{max} (KBr) 3434(w), 1691(m),1639(s),1527(m) and 1456(m)cm^{-1}; δ($CDCl_3$)0.43-0.53(8H,m), 1.26-1.35(2H,m),3.79(3H,s),3.89 (4H,t(overlapping d), J=7.0H_z),4.55(2H,brs),5.32(2H,s),6.90(2H,d,J=9.0H_z)7.30(2H,d,J=9.0H_z); m/e 121(100%), 395(M^+,20);

Found C, 63.64; H, 6.36; N, 17.77. $C_{21}H_{25}N_5O_3$ requires C, 63.78; H, 6.37; N, 17.71%.

Example 3

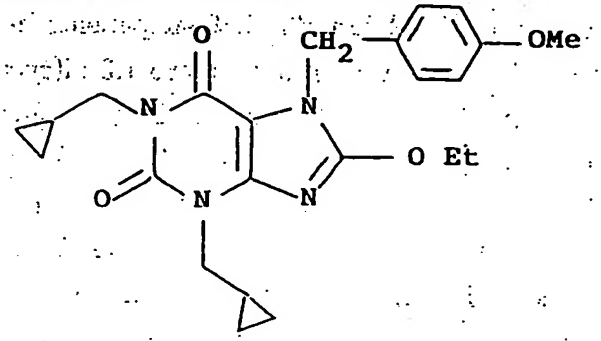
8-Amino-1,3-di(cyclopropylmethyl)-7-methylxanthine



Potassium t-butoxide (1.34g,12mmole) was added to a solution of 8-amino-1,3-di(cyclopropylmethyl)xanthine (2.7g, 10mmole) in DMF (25ml) and the resulting mixture was stirred for 0.5hr at ambient temperature. Methyl iodide (1.78g,0.78ml, 12.5mmole) was added to the red solution, an exothermic reaction resulted and a precipitate formed. After stirring for 10 minutes the mixture was added to ethyl acetate (200ml), washed with dilute hydrochloric acid (50ml), water(50ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a solid which was chromatographed on silica (acetone/hexane gradient) to give 8-amino-1,
3-di(cyclopropylmethyl)-7-methylxanthine (1.5g,52%),
m.p.204-5^{0}C, ν_{max} (KBr) 3405(w), 3343(w), 1689(m),1649(s),
1638(s),1534(m) and 1464(m) cm^{-1}; $\delta(CDCl_3)$
0.41-0.50(8H,m), 1.26-1.36(2H,m), 3.75(3H,s), 3.90m (4H,d,J=7.0H_z),
4.77(2H,brs); m/e 289(M^+,55%),151(30), 55(13),261(12);
Found C, 58.00; H, 6.50; N, 24.08. $C_{14}H_{19}N_5O_2$
requires C, 58.11; H, 6.62; N, 24.21%.

Example 4

1,3-Di(cyclopropylmethyl)-8-ethoxy-7-(4-methoxybenzyl-xanthine



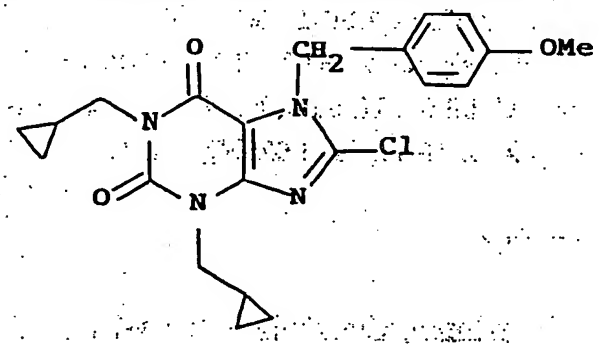
Sodium ethoxide (3ml of a 1M solution in ethanol, 3mmol) was added to a solution of 8-chloro-1,3- di(cyclopropylmethyl)-7-(4-methoxybenzyl)-xanthine (1.0g, 2.4mmol) in dry ethanol (5ml) and the reaction mixture was heated at reflux for 16 hours. The solution was allowed to cool and the solvent was removed under reduced pressure. The residue was suspended in ½% methanol/dichloromethane and the solvent decanted from the sodium chloride.

Purification by column chromatography over silica gel in the same solvent system, afforded 1,3-di(cyclopropylmethyl)-8-ethoxy-7-(4-methoxybenzyl)xanthine (0.87g, 85%) which was recrystallised from ethylacetate-hexane to afford a white crystalline solid, m.p. 112-113°C, ν_{max} (KBr) 2953(m), 2836(s), 1697(s), 1651(s), 1609(s), 1514(s), 1454(s) and 1427(s); ^{1}Hδ (270 MH_Z, $CDCl_3$) 0.45 (8H, m), 1.29 (2H, m), 1.45 (3H, t, J = 7.15Hz), 3.77 (3H, s), 3.87 (2H, d, J = 7.4Hz), 3.90 (2H, d, J = 7.4Hz), 4.52 (2H, q, J = 7.1Hz), 5.20 (2H, s), 6.84 (2H, d, J = 8.8Hz) and 7.42 (2H, d, J = 8.8Hz); m/e 424 (25%, M^+), 121 (100)

Found: C, 65.02; 6.68; N, 13.42. $C_{23}H_{28}N_4O_4$ requires C, 65.07; H, 6.65; N, 13.20%.

Example 5

8-Chloro-1,3-di-(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine

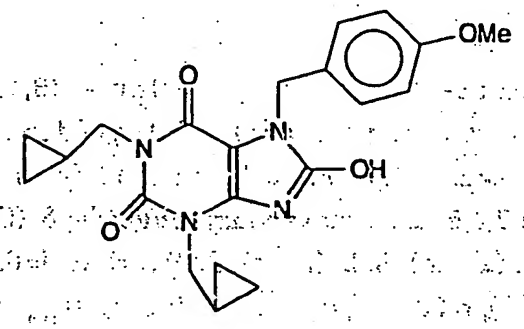


Sodium hydride (2.11g of a 60% suspension in oil, 53mmol) was added portionwise to a solution of 8-chloro-1,3-di(cyclopropylmethyl)xanthine (14.4g, 44mmol) in anhydrous dimethylsulphoxide (100ml). After 1 hour, 4-methoxybenzyl chloride (6.5ml, 48mmol) was added and stirring continued for 16 hours. The reaction mixture was quenched with water (100ml) and extracted into ethyl acetate. The combined organic extracts were washed with water, dried over magnesium sulphate, filtered and concentrated. The solid residue was recrystallised from hexane to afford

8-chloro-1,3- di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine (15.0g, 82%) as a white solid, m.p. 135-136°C, ν_{max} (KBr) 1704(s), 1663(s), 1612(m), 1533(m), 1514(m) and 1453(m) cm^{-1};
$^1H\delta$ (270 MH_z, $CDCl_3$) 0.46 (8H, m), 1.30 (2H, m), 3.78 (3H, s), 3.92 (4H, dd, J = 1.38, 7.2 Hz), 5.48 (2H, s), 6.86 (2H, d, J = 9Hz), 7.42 (2H, d, J = 9Hz); m/e 414 (10%, M^+), 121 (100)
Found: C, 60.57; H, 5.41; N, 13.72. $C_{21}H_{23}N_4O_3Cl$ requires C, 60.8; H, 5.6; N, 13.50%.

Example 6

1,3-Di(cyclopropylmethyl)-8-hydroxy-7-(4-methoxybenzyl)xanthine

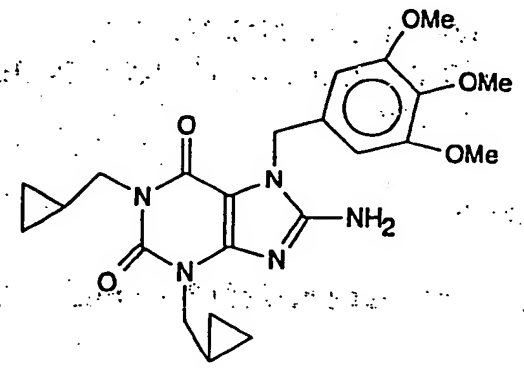


2-Hydroxyethylpyridine (0.32g, 1.1 equiv) was added dropwise to a suspension of 8-chloro-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine (1g, 2.41 mmol) and sodium hydride (0.15g of a 60% dispersion in oil, 1.5 equivs) in dry DMSO (20ml) and was heated at 80°C for 16h. The reaction mixture was poured into water, neutralized and extracted into ethyl acetate (x3). The combined organic solutions were dried, filtered and concentrated. The residue was purified by column chromatography over silica gel in 0.5-1% methanol/dichloromethane to afford 1,3-di(cyclopropylmethyl)-8-hydroxy-7-(4-methoxybenzyl)xanthine (0.4g, 84% based on recovered starting material), mp 247°C (ethyl acetate/chloroform/hexane). δ ($CDCl_3$) 0.39-0.63 (8H,m), 1.23-1.40 (2H,m), 3.77 (3H,s), 3.85 (2H,d J=7.1Hz), 3.89 (2H, d J=7.1Hz), 5.13 (2H,s), 6.83 (2H, d J=8.8Hz), 7.50 (2H, d J=8.8Hz), 13.14 (1H,s).

Found: C, 63.40; H, 6.12; N, 14.00. $C_{21}H_{24}O_4N_4$ requires C, 63.62; H, 6.10; N, 14.13%.

Example 7

8-Amino-1,3-di(cyclopropylmethyl)-7-(3,4,5-trimethoxybenzyl)xanthine

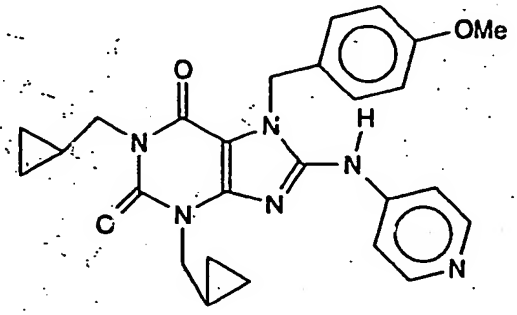


8-Amino-1,3-di(cyclopropylmethyl)-7-(3,4,5-trimethoxybenzyl)xanthine mp 173-174°C was prepared in 84% yield in a similar manner to the compound of Example 2 using 8-amino-1,3-di(cyclopropylmethyl)xanthine and 3,4,5-trimethoxybenzyl chloride; δ ($CDCl_3$) 0.44-0.49 (8H,m), 1.29-1.32 (2H,m), 3.82 (9H,s), 3.89 (2H, d, J=6.9Hz), 3.92 (2H,d, J=6.9Hz), 4.82 (2H,s), 5.30 (2H,s) and 6.57 (2H,s); ν_{max} (KBr) 3414 (m), 1694 (s), 1646 (s), 1633 (s), 1525 (s), 1456 (s) and 1127 (s) cm^{-1}; m/e (FAB) 181 (100%), 456 (M^+,20), observed 455.2169, $C_{23}H_{29}N_5O_5$ requires 455.2156;

Found: C, 60.55; H, 6.23; N, 15.27. $C_{23}H_{29}N_5O_5$ requires C, 60.64; H, 6.42; N, 15.38%.

Example 8

1,3-Di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(4-pyridylamino)xanthine

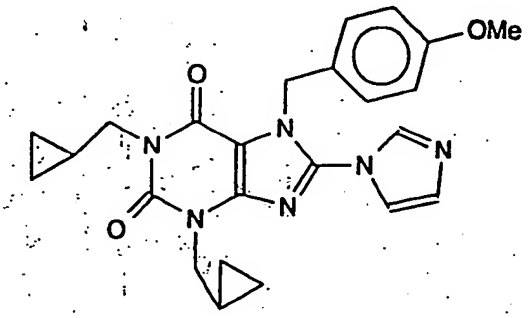


This compound was prepared according to the procedure of Example 9 but with 4-aminopyridine replacing imidazole. Purification by column chromatography afforded 1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(4-pyridylamino)xanthine (35%); mp 207-208°C (decomp, ethylacetate/hexane). δ ($CDCl_2$/DMSO-d_6) 0.32-0.57 (8H,m), 1.26-1.40 (2H,m), 3.19 (1H,brs), 3.74 (3H,s), 3.86 (2H, d J=7.15Hz), 3.96 (2H, d J=7.15Hz), 5.57 (2H,s), 6.82 (2H, d J=8.8Hz), 7.29 (2H, d J=8.8Hz), 7.62 (2H, d J=6.5Hz), 8.36 (2H,brs).

Found: C, 66.28; H, 5.77; N, 17.94. $C_{26}H_{28}N_6O_3$ requires C, 66.08; H, 5.97; N, 17.78%.

Example 9

1,3-Di(cyclopropylmethyl)-8-imidazoyl-7-(4-methoxybenzyl)xanthine



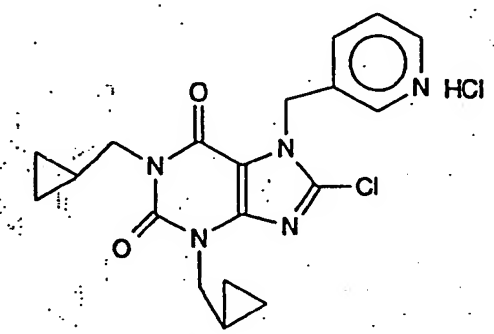
A solution of 8-chloro-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine (0.5g, 1.21 x 10^{-3} moles), potassium t-butoxide (0.15g, 1.1 equiv) and imidazole (0.090g, 1.1 equivs) in dry dimethyl sulphoxide (10ml) was heated at 80°C for 16h. The reaction mixture was allowed to cool, poured into water and extracted into ethyl acetate (x3). The combined organic solutions were dried over magnesium sulphate, filtered and concentrated. The crude residue was purified by column chromatography over silica gel in 1% methanol/dichloromethane to afford 1,3-di(cyclopropylmethyl)-8-imidazoyl-7-(4-methoxybenzyl)xanthine (0.32g, 59%), mp 117-119°C (ethyl acetate/hexane). δ ($CDCl_3$) 0.41-0.56 (8H,m), 1.26-1.40 (2H,m), 3.77 (3H,s), 3.96 (2H,d J=7.1Hz), 3.97 (2H,d J=7.1Hz), 5.48 (2H,s), 6.82 (2H,d J=8.8Hz), 6.98 (2H,d J=8.5Hz), 7.20 (1H,s), 7.26 (1H,s) and 7.78 (1H,s).

Accurate Mass: Found 446.2065. $C_{24}H_{26}N_6O_3$. requires 446.2066.

Found: C, 64.48; H, 5.94; N, 18.81. $C_{24}H_{26}N_6O_3$ requires C, 64.55; H, 5.87; N, 18.82%.

Example 10

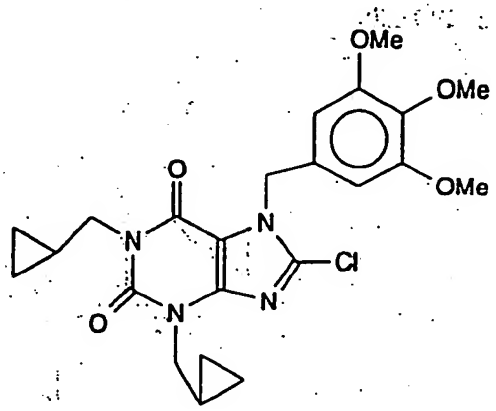
8-Chloro-1,3-di(cyclopropylmethyl)-7-(3 pyridylmethyl)xanthine hydrochloride



8-Chloro-1,3-di(cyclopropylmethyl)-7-(3 pyridylmethyl)xanthine was prepared from 3-chloromethylpyridine and 8-chloro-1,3-di(cyclopropylmethyl)xanthine according to the procedure of Example 14, except that the reaction mixture was heated at 80°C for 16h. The free base was dissolved in dry ether and the solution was saturated with hydrogen chloride gas. 8-Chloro-1,3-di(cyclopropylmethyl)-7-(3-pyridylmethyl)xanthine hydrochloride, m.p. >200°C (methanol/ether), was precipitated. δ (DMSO-d_6) 0.29-0.51 (8H,m), 1.11-1.27 (2H,m), 3.77 (2H,d J=6.8Hz), 3.84 (2H, d J=7.1Hz), 4.5-6.0 (1H, br s), 5.68 (2H,s), 7.83 (1H,t), 8.22 (1H, d J=8.5Hz), 8.76 (1H, d J=4.4Hz), 8.85 (1H,s).
Accurate Mass: Found 386.1365. $C_{19}H_{21}N_5O_2Cl$ (MH^+) requires 386.1384.
Found: C,53.82; H, 5.17; N, 16.60. $C_{19}H_{21}N_5O_2Cl_2$ requires C, 54.03; H, 5.01; N, 16.58%.

Example 11

8-Chloro-1,3-di(cyclopropylmethyl)-7-(3,4,5-trimethoxybenzyl)xanthine

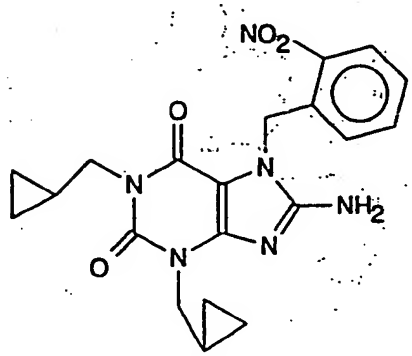


8-Chloro-1,3-di(cyclopropylmethyl)-7-(3,4,5-trimethoxybenzyl)xanthine, m.p. 109-110°C, was prepared in 62% yield from 3,4,5-trimethoxybenzyl chloride and 8-chloro-1,3-di(cyclopropylmethyl)xanthine using the procedure of Example 14. δ ($CDCl_3$) 0.42-0.51 (8H, m), 1.25-1.36 (2H, m), 3.82 (3H, s), 3.84 (6H, s), 3.93 (4H, 2xd J=7.15Hz), 5.45 (2H, s), 6.82 (2H, s)

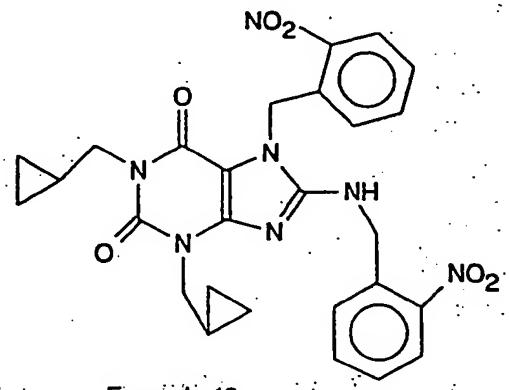
Found: C, 58.33; H, 5.47; N, 11.72. $C_{23}H_{27}N_4O_5Cl$ requires C, 58.16; H, 5.73; N, 11.80%.

Examples 12 and 13

8-Amino-1,3-di(cyclopropylmethyl)-7-(2-nitrobenzyl)xanthine (Example 12) and 1,3-Di(cyclopropylmethyl)-8-(2-nitrobenzylamino)-7-(2-nitrobenzyl)xanthine (Example 13)



Example 12



Example 13

8-Amino-1,3-di(cyclopropylmethyl)xanthine was reacted with 2-nitrobenzyl bromide in a similar manner to that for the compound of Example 2 to give, after chromatography on silica (hexane/acetone gradient), 1,3-di(cyclopropylmethyl)-8-(2-nitrobenzylamino)-7-(2-nitrobenzyl)xanthine (14%), m.p. 198-9°C; δ ($CDCl_3$) 0.32-0.58 (8H, m), 1.17-1.13 (1H, m), 1.33-1.40 (1H, m), 3.82 (2H, d, J=7.1Hz), 3.94 (2H, d, J=7.1Hz), 4.83 (2H, d, J=6.1Hz), 5.63 (1H, t, J=6.3Hz), 5.73 (2H, s), 7.03 (1H, d, J=7.7Hz), 7.42-7.64 (5H, m), 7.83 (1H, d, J=8.0Hz), 8.10 (1H, d, J=8.0Hz); ν_{max} (KBr) 1695(s), 1652(s), 1619(s), 1570(m), 1526(s), 1476(m), 1340(m), 1302(m), 1275(m) and 727(m) cm^{-1}; m/e (FAB) 546 (MH^+, 100%), 136(43), 55(28), 91(15), 78(12), and 530(10);

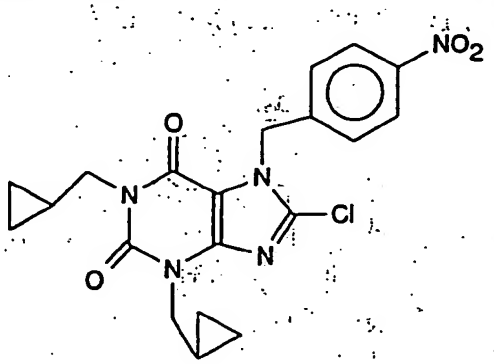
Found: C, 59.16; H, 5.04; N, 18.08. $C_{27}H_{27}N_7O_6$ requires C, 59.44; H, 4.99; N, 19.97%

followed by 8-amino-1,3-di(cyclopropylmethyl)-7-(2-nitrobenzyl)xanthine (22%), m.p. 240-1°C, δ ($CDCl_3$) 0.35-0.42 (4H, m), 0.45-0.53 (4H, m), 1.21-1.36 (1H, m), 1.37-1.42 (1H, m), 3.82 (2H, d, J=7.1Hz), 3.93 (2H, d, J=7.1Hz), 5.83 (2H, s), 6.05 (2H, brs), 6.94 (1H, dd, J=1.1, 8.0Hz), 7.11-7.62 (2H, m), 8.17 (1H, dd, J=1.1, 8.0Hz) ν_{max} (KBr) 1695(s), 1638(s), 1525(s), 1452(s), 1338(m), 1275(m) and 728(w) cm^{-1}; m/e (FAB) 411 (MH^+, 100%), 55(50), 136(35), 357(18), 91(14);

Found: C, 58.30; H, 5.43; N, 20.55. $C_{20}H_{22}N_6O_4$ requires C, 58.52; H, 5.40; N, 20.48%.

Example 14

8-Chloro-1,3-di(cyclopropylmethyl)-7-(4-nitrobenzyl)xanthine

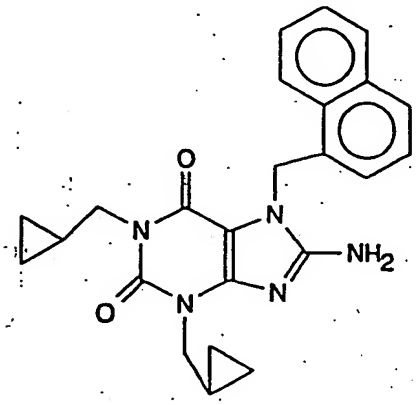


Sodium hydride (0.16g of a 60% suspension in oil, 1.2 equivs) was added to a solution of 8-chloro-1,3-di(cyclopropylmethyl)xanthine (1g, 3.40 x 10^{-3} moles) in dry DMSO (25ml). After 1 h, 4-nitrobenzyl bromide (0.88g, 1.2 equivs) was added and the solution was stirred at ambient temperature for 16 h. The reaction mixture was poured into water and extracted into ethyl acetate (x3). The combined organic solutions were dried, filtered and concentrated. The crude residue was purified by column chromatography over silica gel in 1% methanol/dichloromethane to afford 8-chloro-1,3-di(cyclopropylmethyl)-7-(4-nitrobenzyl)xanthine (0.93g, 64%) as a white solid m.p. 111-112°C (ethyl acetate/hexane). δ ($CDCl_3$) 0.38-0.55 (8H,m), 1.22-1.39 (2H,m), 3.90 (2H,d J=7.15Hz), 3.95 (2H, d J=7.15Hz) 6.4 (2H,s), 7.58 (2H,d J=8.8Hz), 8.23 (2H, d J=8.8Hz). Accurate Mass: Found 430.1285. $C_{20}H_{21}N_5O_4Cl$ (MH^+) requires 430.1282.

Found C,55.91; H, 4.81; N, 16.22. $C_{20}H_{20}N_5O_4Cl$ requires C,55.88; H,4.69; N, 16.29%.

Example 15

8-Amino-1,3-di(cyclopropylmethyl)-7-(1-naphthylmethyl)xanthine

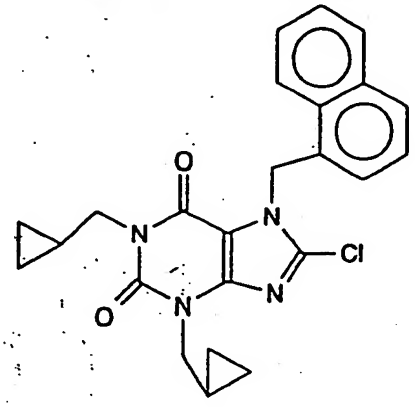


Potassium t-butoxide (0.48g, 1.2equiv) was added to a suspension of 8-amino-1,3-di(cyclopropylmethyl)xanthine (1g, 3.63×10^{-3} moles) in dry ethylene glycol dimethyl ether (25ml). After 0.5h 1-chloromethylnaphthalene (0.77g, 1.2 equivs) was added and stirring continued for a further 16 h. The reaction mixture was poured into water, neutralised, and extracted into ethyl acetate (x3). The combined organic extracts were dried over magnesium sulphate, filtered and concentrated. The crude residue was purified by column chromatography over silica gel in 1% methanol/dichloromethane to afford 8-amino-1,3-di(cyclopropylmethyl)-7-(1-naphthylmethyl)xanthine (0.82g, 54%) as a pale pink solid m.p. 215-216°C. δ ($CDCl_3$) 0.33-0.56 (8H,m), 1.2-1.44 (2H,m), 3.82 (2H,d J=7.15Hz), 3.93 (2H,d J=7.15Hz), 5.67 (2H,br s), 5.90 (2H,s), 6.96 (1H,d J=7.1Hz), 7.40 (1H,t J=7.1Hz), 7.55 (2H,m), 7.79 (1H,d J=8.2Hz), 7.85 (1H,d), 8.07 (1H,d).

Accurate Mass: Found 416.2066. $C_{24}H_{26}N_5O_2$ (MH^+) requires 416.2087.

Example 16

8-Chloro-1,3-di(cyclopropylmethyl)-7-(1-naphthylmethyl)xanthine



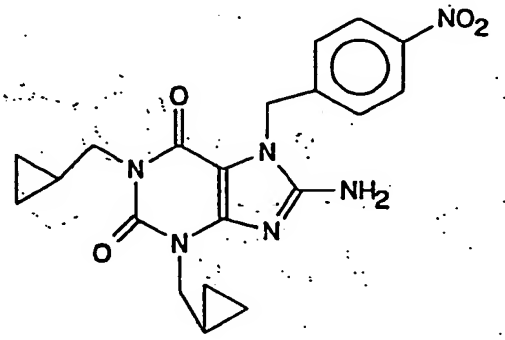
8-Chloro-1,3-di(cyclopropylmethyl)-7-(1-napthylmethyl)xanthine, m.p. 187-188°C (hexane), was prepared in 32% yield from 1-chloromethylnaphthalene and 8-chloro-1,3-di(cyclopropylmethyl)xanthine using the procedure of Example 14. δ ($CDCl_3$), 0.37-0.59 (8H,m), 1.21-1.46 (2H,m), 3.87 (2H,d J=7.14Hz), 4.01 (2H,d J=7.14Hz), 6.10 (2H,s), 6.76 (1H, d J=7.14Hz), 7.38 (1H,t), 7.58 (2H,m), 7.81 (1H, d J=8.3Hz), 7.91 (1H, d J=7.7Hz), 8.06 (1H,d J=8.2Hz).

Found C,66,14; H, 5.23; N, 12.85. $C_{24}H_{23}N_4O_2Cl$ requires C,66.27; H, 5.32; N, 12.80%.

Accurrate Mass: Found 435.1588. $C_{24}H_{23}N_4O_2Cl$ requires 435.1588.

Example 17

8-Amino-1,3-di(cyclopropylmethyl)-7-(4-nitrobenzyl)xanthine

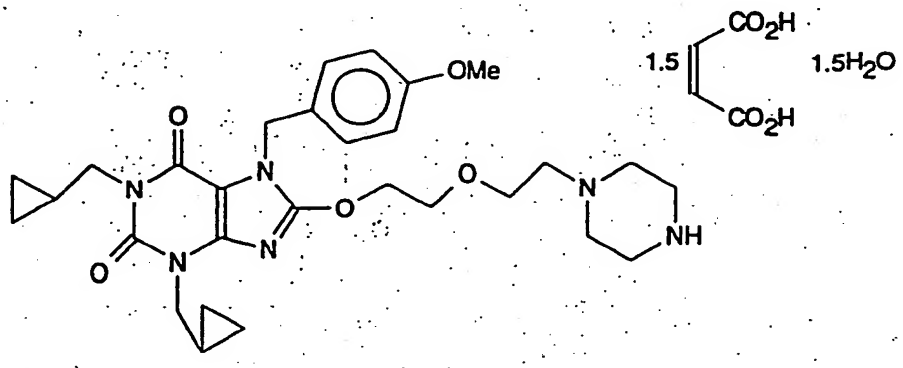


Sodium hydride (0.17g of a 60% dispersion in oil, 1.2 equivs) was added to a suspension of 8-amino-1,3-di(cyclopropylmethyl)xanthine (1g, 3.63 x 10^{-3} moles) in dry DMSO (25ml). After stirring for 1 h at ambient temperature 4-nitrobenzyl bromide (0.94g, 1.2 equivs) was added. After 16 h the reaction mixture was poured into water, neutralised and extracted with ethyl acetate (x3). The combined organic extracts were dried over magnesium sulphate, filtered and concentrated. The crude residue was purified by column chromatography over silica gel in 2% methanol/dichloromethane to afford 8-amino-1,3-di(cyclopropylmethyl)-7-(4-nitrobenzyl)xanthine (1.03g, 69%) as a pale yellow solid, m.p. 136-137°C. δ ($CDCl_3$) 0.36-0.54 (8H,m), 1.23-1.39 (2H,m), 3.88 (4H,t,J=6.75Hz), 4.59 (2H,s), 5.47 (2H,s), 7.47 (2H,d,J=8.8Hz), 8.21 (2H,d of t J=8.8Hz).

Accurate Mass: Found 411.1781. $C_{20}H_{23}N_6O_4$ (MH^+) requires 411.1781.

Example 18

1,3-Di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-[2-(2-[*N*-piperizinyl]ethoxy)ethoxy]xanthine sesquimaleate sesquihydrate



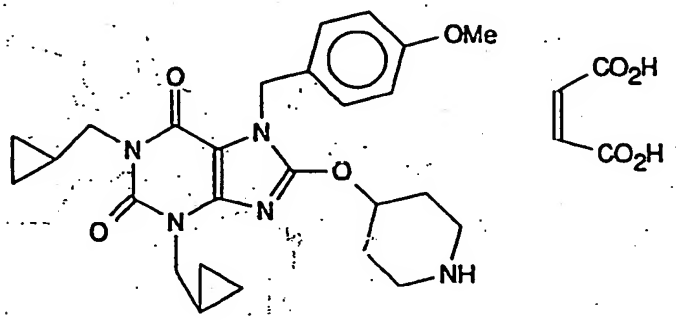
This compound was prepared according to the procedure of Example 6 using 2-(2-(N-piperizinyl)ethoxy)ethanol and 8-chloro-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl]xanthine. Purification by column chromatography over silica gel using 4% methanol/dichloromethane afforded 1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-[2-(2-[*N*-piperizinyl]ethoxy)ethoxy]xanthine (44%) as an oil. δ ($CDCl_3$) 0.43-0.48 (8H, m), 1.29 (2H, m), 1.95 (1H, brs), 2.50(4H, m), 2.60 (2H, t, J=5.8Hz), 2.90 (4H, t), 3.66 (2H, t, J=5.8Hz), 3.77 (3H, s), 3.77-3.91 (6H, m), 4.61 (2H, t), 5.22 (2H, s), 6.83 (2H, d, J=8.5Hz), 7.44 (2H, d, J=8.5Hz);

Accurate Mass: Found: 552.5878 $C_{29}H_{40}N_6O_5$ requires 552.3060

Treatment of the above oil with maleic acid gave the sesquimaleate sesquihydrate m.p. 150-5°C (decomp. ethanol/diisopropyl ether).

Example 19

1,3-Di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(4-piperidinyloxy)xanthine maleate

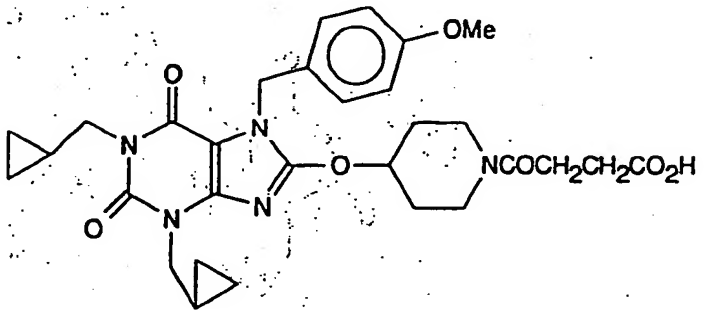


1,3-Di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(4-piperidinyloxy)xanthine maleate was prepared according to the procedure of Example 6 but with 4-hydroxypiperidine replacing 2-hydroxyethylpyridine. Purification by column chromatography over silica gel afforded 1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(4-piperidinyloxy)xanthine (50%) as an oil. δ (DMSO-d_6) 0.31-0.48 (8H,m), 1.15-1.23 (2H,m), 1.54-1.66 (2H,m), 1.93 (2H,m), 2.51-2.62 (2H,m), 2.87-2.94 (2H,m), 3.72 (3H,s), 3.77 (2H,d J=7.15Hz) 3.78 (2H, d J=7.15Hz), 4.95-5.01 (1H,m) 5.16 (2H,s), 6.90 (2H, d J=8.8Hz), 7.30 (2H, d J=8.8Hz). The maleate salt was prepared and recrystallised from methanol/diisopropyl ether to afford the pure material, mp 165-166°C.

Found: C, 60.34; H, 6.39; N, 11.77 $C_{30}H_{37}O_8N_5$ requires C, 60.49; H, 6.26; N, 11.76%.

Example 20

4-[4-(8-[1,3-Di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthinyloxy]piperidinyl)]-4-oxo-butanoic acid hemihydrate

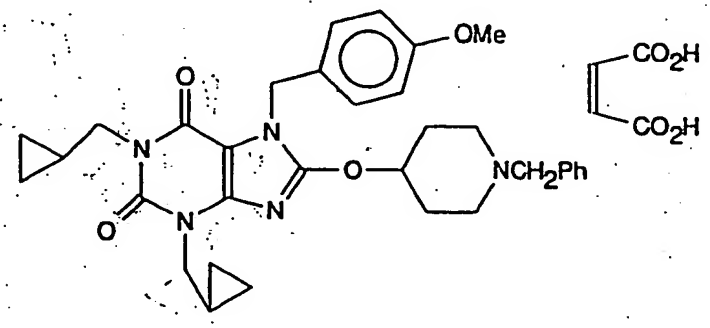


Succinic anhydride (0.23g, 1.2 equivs) was added to a solution of 1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(4-piperidinyloxy)xanthine (0.92g, 1.92 mmoles) in dry THF (20ml). After 48h the solvent was removed by evaporation to give 4-[4-(8-[1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthinyloxy]piperidinyl)]-4-oxo-butanoic acid hemihydrate (0.62g, 56%), mp 141-142°C (ethyl acetate/hexane). δ ($CDCl_3$) 0.43-0.52 (8H,m), 1.25-1.29 (2H,m), 1.91-2.02 (4H,m), 2.71 (4H,m), 3.49-3.71 (5H,m), 3.77 (3H,s), 3.87 (2H,d J=7.4Hz), 3.91 (2H, d J=7.2Hz), 5.23 (3H,m), 6.85 (2H, d J=8.8Hz), 7.37 (2H, d J=8.5Hz).

Found: C, 60.82; H, 6.32; N, 11.82 $C_{30}H_{37}O_7N_5$ $0.5H_2O$ requires C, 61.20; H, 6.50; N, 11.89%.

Example 21

8-[4-(*N*-Benzyl)piperidinyloxy]-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine maleate



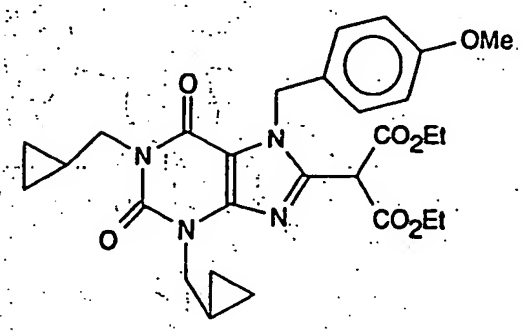
Benzyl bromide (0.17g, 1.2 equivs), triethylamine (0.21g, 2.5 equivs), and 1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(4-piperidinyloxy)xanthine (0.40g, 8.4×10^{-4} mmole) were stirred in dry tetrahydrofuran (10ml) for 16h. The reaction mixture was poured into aqueous sodium bicarbonate solution and extracted into dichloromethane. The combined organic solutions were dried over magnesium sulphate, filtered and concentrated and the residue was purified by column chromatography over silica gel in 1% methanol/dichloromethane to afford 8-[4-(*N*-benzyl)piperidinyloxy]-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine (0.36g, 76%). δ ($CDCl_3$) 0.43-0.48 (8H,m), 1.26-1.32 (2H,m), 1.86-1.94 (2H,m), 2.03-2.09 (2H,m), 2.35-2.41 (2H,m), 2.66 (2H,m), 3.54 (2H,s), 3.78 (3H,s), 3.87 (2H, d J=11.82Hz), 3.90 (2H, d J=11.5Hz), 5.00-5.21 (1H,m), 5.20 (2H,s), 6.85 (2H, d J=8.79Hz), 7.26-7.39 (5H,m) and 7.42 (2H, d J=8.8Hz). Accurate Mass: Found 569.2919. $C_{33}H_{39}N_5O_4$ requires 569.3002.

The maleate salt was prepared and recrystallised from methanol/diisopropyl ether to afford the pure material as a white solid mp 160-161°C.

Found: C, 64.71; H, 6.42; N, 9.93. $C_{37}H_{43}O_8N_5$ requires C, 64.80; H, 6.32; N, 10.21%.

Example 22

Diethyl 8-[1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthin-yl]malonate



Sodium hydride (1.48g of a 60% suspension in oil, 37 mmol) was added portionwise to a solution of diethyl malonate (5.4g, 34 mmol) in anhydrous DMSO (70 ml) and stirring continued for 1h at ambient temperature. 8-Chloro-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine (7.0g, 16.9 mmol) was added and the reaction mixture was heated to 80 °C. After 16h the solution was allowed to cool, poured into water and extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel in 0.5% methanol/dichloromethane to afford diethyl 8-[1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthinyl]malonate (8.95g, 98%), m.p. 134-135°C δ ($CDCl_3$) 0.39-0.50 (8H,m), 1.22 (6H, t, J=7.1Hz), 1.31 (2H, m), 3.77 (3H, s), 3.92 (2H, d, J=7.1Hz), 3.95 (2H, d, J=7.1Hz), 4.14 (4H, m), 4.79 (1H, s), 5.52 (2H, s), 6.85 (2H, d, J=8.8Hz), 7.13 (2H, d, J=8.8Hz). Found: C, 62.40; H, 6.39; N, 10.35. $C_{28}H_{34}N_4O_5$ requires C, 62.40; H, 6.30; N, 10.4%

Procedure 1

1,3-Di-cyclopropylmethyl-8-nitro xanthine

1,3-Di-cyclopropylmethyl xanthine (20g, 0.076mol) was dissolved in acetic acid (33ml) and then treated with concentrated nitric acid (13.2g) at 87°C. After 1 hour, the mixture was cooled to 5°C and the resulting yellow precipitate filtered off. The yellow crystals were dissolved in dichloromethane and washed with water. The separated organic layer was then dried over anhydrous sodium sulphate and concentrated in vacuo. The product crystallized from the concentrate to yield a yellow crystalline product yield 12.2g, (56.5%), m.p. 207°C (with decomposition). ^{1}H NMR ($CDCl_3$):

ppm: 0.35-0.7 (m, 8H), 1.1 -1.7 (m, 2H), 3.95-4.2 (m, 4H), 9.0-11.0 (br. exchanges with D_2O, 1H).

Procedure 2

1,3-Di-cyclopropylmethyl-8-amino xanthine

1,3-Di-cyclopropylmethyl-8-nitro xanthine (4g, 0,014mol), suspended in 50ml of concentrated hydrochloric acid,was treated with small portions of tin (8g) at room temperature. The mixture was then stirred at room temperature for two hours.

The resulting precipitate was filtered off and crystallised from ethanol to give white crystals of the title product, yield 0.9g (23%), m.p. 281°C.

In an alternative procedure, using sodium dithionite as reducing agent (in methanol-water mixture). The yield was 36% (compare Example 13).

^{1}H NMR ($CDCl_3$):

ppm: 0.3-0.6 (m,8H), 1.0-1.6 (m,2H), 3.7-4.0 (m,4H), 5.75 (br,2H), 10.84 (br. exchanges with D_2O, 1H).

Preparation 3

8-Chloro-1,3-di(cyclopropylmethyl)xanthine

1,3-Di(cyclopropylmethyl)-8-nitroxanthine (50g, 164mmol) was dissolved in dry dimethylformamide (300ml) and to this phosphorus oxychloride (50ml, 536mmol) was added dropwise with caution. After 16h, the reaction mixture was poured onto ice and the precipitate was collected and washed with water. The solid was dissolved in dichloromethane, and dried ($MgSO_4$). The solution was filtered and concentrated and the crude product was recrystallised from ethyl acetate/hexane to afford 8-chloro-1,3-di(cyclopropylmethyl)xanthine (31g, 64%) as a white crystalline solid. ^1H NMR ($CDCl_3$/DMSO-d6) d 0.40-0.53 (8H, m), 1.31 (2H, m), 2.76 (1H, br.s), 3.89 (2H, d, J = 7.15Hz), 3.94 (2H, d, J = 7.42Hz); ν_{max} (KBr) 3438(s), 1707(s), 1648(s), 1601(m), 1545(s), and 1465(s) cm^{-1}; m/e 294 (40%, M^+), 55 (100)
Found: C, 52.97; H, 5.04; N, 19.02. $C_{13}H_{15}N_4ClO_2$ requires C, 52.97; H, 5.09; N, 19.01%.

PHARMACOLOGICAL DATA

1) Induction of blood eosinophilia and the effects of drugs.

Animals

Male Charles River Sprague Dawley rats weighing between 270 to 400g were used.

The method used was a modification of that described by Laycock et al (Int. Arch. Appl. Immunol, (1986). 81, 363).

Sephadex G200, particle size 40 to 120 micron, was suspended in isotonic saline at 0.5mg/ml, and stored for 48h at 4°C. 1ml of the suspension was given intravenously to rats on days 0,2 and 5. A control group received saline. The test compound was given before the Sephadex on each occasion, with a contact time expected to give maximum activity at the time of the Sephadex administration. Blood was taken from the tail vein of the rats on day 7 for the determination of total and differential leucocyte counts.

A control group of at least 6 animals was included each time a compound was evaluated. The control group received Sephadex and the vehicle without test compound. The results in the drug treated animals were compared with the control group.

Total and differential leucocyte counts.

20ml samples of blood, taken from the tail vein of the rats, were added to 10ml of Isoton II and, within 30min, Zaponin (3 drops) was added, to lyse the erythrocytes. Five minutes later the total cell count was determined using a Coulter Counter Model DN. Differential leucocyte counts were carried out by fixing and staining a blood smear on a microscopic slide with May-Grunwald and Giemsa stains. A minimum of 400 cells were counted on each slide.

Statistics

Probability values were calculated using the Student's t test.

Results

The effect of the test compound upon Sephadex induced eosinophilia in the rat is set out below. The test compound was given orally 30 minutes before each injection of Sephadex.

Test Compound	Dose mg/kg (orally - 30 mins)	% of Control Mean ± SEM (n=16
Vehicle dosed control + sephadex i.v	-	100 ± 13
Negative control saline i.v.		14 ± 1 ***
Example 2	10	49 ± 13*
Example 3	20	60± 12*

Notes

* $p < 0.05$

*** $p < 0.001$

2) Inhibition of Phosphodiesterase

Isolation of phosphodiesterases

The Ca^{2+}/calmodulin-stimulated PDE (PDE I, see Table 1 and Beavo and Reifsynder (1990) for nomenclature) was prepared from bovine cardiac ventricle. Following chromatography on a Mono Q column, the fractions showing stimulation of PDE activity by Ca^{2+} and calmodulin were pooled and further purified on a calmodulin-affinity column. cGMP-stimulated PDE (PDE II), cGMP-inhibited PDE (PDE III) and cAMP-specific PDE (PDE IV) were all isolated from guinea-pig cardiac ventricle. Initial chromatography on a 20 ml Mono Q column resolved PDE III from a peak that contained both PDE II and PDE IV. The latter were separately rechromatographed on a 1 ml Mono Q column. cGMP-selective PDE (PDE V) was obtained from porcine lung using chromatography on DEAE-cellulose and Mono Q columns; a calmodulin-affinity column was used to remove residual PDE I activity.

Characteristics of phosphodiesterase isoenzymes

With the exception of PDE II, which displayed positive cooperativity, all the preparations showed simple Michaelis-Menton kinetics (see Table 1).

PDE I The activity of this isoenzyme was stimulated by the Ca^{2+}-calmodulin complex. The isoenzyme could hydrolyse both cAMP and cGMP, the latter was the preferred substrate.

PDE II The activity of this isoenzyme with cAMP as a substrate was stimulated by cGMP. The isoenzyme could hydrolyse both cAMP and cGMP, the latter was the preferred substrate under basal conditions. The activity of this isoenzyme was unaffected by the Ca^{2+}-calmodulin complex.

PDEIII The activity of this isoenzyme with cAMP as a substrate was inhibited by cGMP. The isoenzyme could hydrolyse both cAMP and cGMP, the former was the preferred substrate. The activity of this isoenzyme was unaffected by the Ca^{2+} calmodulin complex.

PDE IV This isoenzyme had high affinity for cAMP, the hydrolysis of which was not inhibited by cGMP. The activity of this isoenzyme was unaffected by the Ca2-calmodulin complex.

PDE V This isoenzyme had high affinity for cGMP. The activity of this isoenzyme was unaffected by the Ca^{2+}-calmodulin complex.

Assay of phosphodiesterase activity

PDE activity was assayed by the boronate column method as previously described (Reeves et. al., 1987). The enzymes were assayed by incubation at 37°C for 4-30 min. in 50 mM Tris, 5 mM $MgCl_2$, pH 7.5 with ^3H-labelled cyclic nucleotide (4×10^5 disintegrations min^{-1}) and ^{14}C-labelled nucleotide 5'-monophosphate (3×10^3 disintegrations min^{-1}). The assay was stopped by boiling and the ^3H-labelled 5'-monophosphate product separated from substrate on boronate columns. The reaction mixture was diluted with 0.5 mL 100 mM HEPES [N-(2-hydroxyethyl)piperazine-N^1-2-ethanesulfonic acid], 100 mM NaCl, pH 8.5, and applied to the column. The column was extensively washed with the same buffer, and the 5'-nucleotide eluted with 6 mL of 0.25 M acetic acid. The recovery of product as judged by ^{14}C-recovery was approximately 80%. All assays were linear with time of incubation and concentration of enzyme over the range used in these experiments. IC_{50} values (the concentration of inhibitor required for 50% inhibition of activity) were obtained by incubation of the isoenzyme using 1 mM cGMP as a substrate for PDE I (in the absence of Ca^{2+} and calmodulin), PDE II and PDE V and with 1 mM cAMP as a substrate for PDE III and PDE IV. A range of inhibitor concentrations from $0.1 \times IC_{50}$ to $100 \times IC_{50}$ was used.

References

BEAVO, J.A. and D.H. REIFSNYDER, Primary sequence of cyclic nucleotide phosphodiesterase isozymes and the design of selective inhibitors. Trends. Pharmacol. Sci. 11, 150-155 (1990).

REEVES M.L., B.K. LEIGH and P.J. ENGLAND, The identification of a new cyclic nucleotide phosphodiesterase activity in human and guinea-pig cardiac ventricle. Biochem. J. 241, 535-541 (1987).

Table 1: Kinetic properties of phosphodiesterase isoenzymes

Isoenzyme		Km (μM) cAMP	Km (μM) cGMP	Vmax cAMP / Vmax cGMP
I.	Ca^{2+}/calmodulin-stimulated	36	5	5
II.	cGMP-stimulated	45	14	1
III.	cGMP-inhibited	0.5	0.1	5
IV.	cAMP-specific	2	>	n.d.
V.	cGMP-specific	>	1	N.d.

a enzyme displayed positive cooperativity

> Km > 100 mM

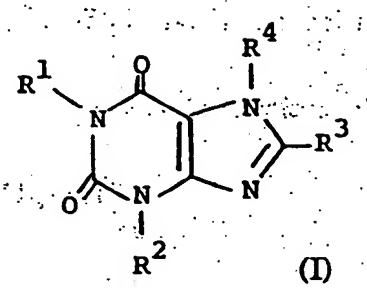
n.d. not determined, due to inability of PDE to hydrolyse one of the substrates.

RESULTS

Example No.	Inhibition of: PDE IV IC_{50} (μM)	PDE V IC_{50} (μM)
1	7.0	0.8
2	3.0	1
3	17	20.0
4	2.0	0.1
5	0.8	0.08

Claims

1. A compound of formula (1):



(I)

or, if appropriate, a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, wherein R^1 and R^2 each independently represent a moiety of formula (a):

$$-(CH_2)_m-A \qquad (a)$$

wherein m represents zero or an integer 1, 2 or 3 and A represents a substituted or unsubstituted cyclic hydrocarbon radical;
R^3 represents NO_2, a halogen atom, a hydroxy group, an alkoxy group or a methyl group substituted with 1 or 2 groups of formula CO_2R wherein R in each group is independently hydrogen or alkyl or a group of formula $O\text{-}L\text{-}A^1$ wherein L is a bond or a linking group and A^1 is a saturated or unsaturated heterocyclic group, or R^3 represents a group of formula NR^sR^t wherein R^s and R^t each independently represent hydrogen, alkyl, aralkyl, an unsaturated heterocyclic group or R^s and R^t together with the nitrogen to which they are attached form an unsaturated heterocyclic group; and
R^4 represents an alkyl, aralkyl or an (unsaturated heterocyclyl)alkyl group.

2. A compound according to claim 1, wherein A represents a substituted or unsubstituted C_{3-8} cycloalkyl group.

3. A compound according to claim 1 or claim 2, wherein A represents an unsubstituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

4. A compound according to any one of claims 1 to 3, wherein A represents a cyclopropyl group.

5. A compound according to any one of claims 1 to 4, wherein R^3 represents nitro, a halogen atom, an alkoxy group, or a group NR^sR^t wherein R^s and R^t each independently represent hydrogen or alkyl.

6. A compound according to any one of claims 1 to 5, wherein R^3 represents NH_2.

7. A compound according to any one of claims 1 to 6, wherein R^4 is an alkyl or aralkyl group.

8. A compound according to any one of claims 1 to 7, wherein R^4 represents benzyl.

9. A compound according to claim 1, selected from the group consisting of:

8-amino-7-benzyl-1,3-di(cyclopropylmethyl)xanthine;

8-amino-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-xanthine;

8-amino-1,3-di(cyclopropylmethyl)-7-methylxanthine;

1,3-di(cyclopropylmethyl)-8-ethoxy-7-(4-methoxybenzyl-xanthine;

8-chloro-1,3-di-(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine;

1,3-di(cyclopropylmethyl)-8-hydroxy-7-(4-methoxybenzyl)xanthine;

8-amino-1,3-di(cyclopropylmethyl)-7-(3,4,5-trimethoxybenzyl)xanthine;

1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(4-pyridylamino)-xanthine;

1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(4-pyridylamino)-xanthine;

8-chloro-1,3-di(cyclopropylmethyl)-7-(3 pyridylmethyl)xanthine hydrochloride;

8-chloro-1,3-di(cyclopropylmethyl)-7-(3,4,5-trimethoxybenzyl)xanthine;

8-amino-1,3-di(cyclopropylmethyl)-7-(2-nitrobenzyl)xanthine

1,3-di(cyclopropylmethyl)-8-(2-nitrobenzylamino)-7-(2-nitrobenzyl)-xanthine;

8-chloro-1,3-di(cyclopropylmethyl)-7-(4-nitrobenzyl)xanthine;

8-amino-1,3-di(cyclopropylmethyl)-7-(1-naphthylmethyl)xanthine;

8-chloro-1,3-di(cyclopropylmethyl)-7-(1-naphthylmethyl)xanthine;

8-amino-1,3-di(cyclopropylmethyl)-7-(4-nitrobenzyl)xanthine;

1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-[2-(2-[N-piperizinyl]ethoxy)ethoxy]xanthine;

1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)-8-(4-piperidinyloxy)xanthine maleate;

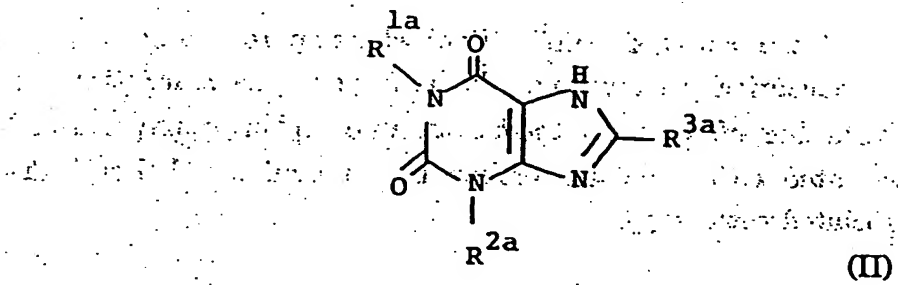
4-[4-(8-[1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthinyloxy]piperidinyl)]-4-oxo-butanoic acid;

8-[4-(N-benzyl)piperidinyloxy]-1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthine maleate; and

diethyl 8-[1,3-di(cyclopropylmethyl)-7-(4-methoxybenzyl)xanthinyl]malonate; or if appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof.

10. A process for the preparation of a compound of formula (I); or where appropriate, a pharmaceutically acceptable salt thereof; or a

pharmaceutically acceptable solvate thereof, which process comprises reacting a compound of formula (II):



(II)

wherein R^{1a} represents R^1, as defined in relation to formula (I), or a group convertible to R^1 and R^{2a} represents R^2, as defined in relation to formula (I), or a group convertible thereto and R^{3a} represents R^3 as defined in relation to formula (I), or a group convertible thereto, with a compound of formula (III):

$$R_4\text{-}L^1 \qquad \text{(III)}$$

wherein R^4 is as defined in relation to formula (I) and L^1 represents a leaving group; and thereafter, if required carrying out one or more of the following optional steps:

(i) converting any group R^{1a} to R^1 and/or R^{2a} to R^2 and/or R^{3a} to R^3;

(ii) converting a compound of formula (I) into a further compound of formula (I);

(iii) converting a compound of formula (I) into a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof.

11. A pharmaceutical composition comprising a compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier.

12. A compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

13. A compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of disorders associated with increased numbers of eosinophils, and allergic disorders associated with atopy.

14. A compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for use as a phosphodiesterase inhibitor.

15. The use of a compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment of and/or prophylaxis of disorders associated with increased numbers of eosinophils, and allergic disorders associated with atopy.

16. The use of a compound of formula (I); or where appropriate a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for use as a phosphodiesterase inhibitor.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01633

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 473/06, A 61 K 31/52

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A,P	EP, A2, 0389282 (BEECHAM - WUELFING GMBH & CO. KG ET AL) 26 September 1990, see the whole document	1-14
A	EP, A2, 0369744 (BEECHAM WUELFING GMBH & CO KG) 23 May 1990, see the whole document	1-14
A	WO, A1, 8805775 (SANDOZ-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H.) 11 August 1988, see the whole document	1-14

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10th December 1991	13 JAN 1992
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme N. KUIPER

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 91/01633

SA 51702

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 31/10/91 The European Patent office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A2- 0389282	26/09/90	AU-D-	5208390	27/09/90
		CN-A-	1047502	05/12/90
		JP-A-	2273676	08/11/90
EP-A2- 0369744	23/05/90	AU-D-	4466789	17/05/90
		JP-A-	2178283	11/07/90
WO-A1- 8805775	11/08/88	AU-B-	600021	02/08/90
		AU-D-	7744587	03/03/88
		EP-A-	0258191	02/03/88

For more details about this annex : see Official Journal of the European patent Office, No. 12/82

EPO FORM P0479